Department of Defense Comments on Toxicological Review of Trimethylbenzenes Final Draft (Step 6b)

Comments submitted by: OASD(EI&E), ESOH Directorate, CMRM Program	Organization: Department of Defense	Date Submitted: 6/29/2016

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	2, Preamble	xvi, line 40	The response to the SAB comments on the Preamble states that the Preamble directs users to the IRIS' guidance website, we do not see this in the Preamble. The IRIS website is mentioned but not in terms of guidance.	Suggest adding specifically noting that links to guidance used are on the IRIS website and note the page.	S
2	1, Preamble	xvi, Line 44	Text was deleted from the Preamble that listed the parties whom EPA requests nominations. The rationale is not evident and makes us wonder whether there are changes planned or have been undertaken to seek nominations for IRIS assessments. The change also seems to run counter to the SAB comment that the Scope section of the Preamble lacks description of IRIS' purpose and what the assessments are meant to represent to users.	If changes have been made to the nomination process it would be useful for us get some information relative to the new process. To incorporate the SAB's recommendations, suggest listing whom nominations are generally solicited and received from.	S
3	2, Preamble	xvi - xvii	There have been changes made to the text in this section that make it sound rather insular and emphasize EPA's needs alone rather than	Please consider revising the statements which focus on "EPA's needs" and "..questions of	O/M

			EPA in addition to its stakeholders. Though we understand that EPA may wish to keep their own needs at the forefront, we would like to remind EPA that States, the public and other Federal agencies use the outcomes of IRIS assessments regardless of whether there is EPA involvement or oversight of those projects or programs. We believe that broader consideration of the use of IRIS assessments would better meet the intent of the SAB comments on the Preamble regarding IRIS' purpose and what the assessments mean to users.	interest to the EPA" to better reflect the reality that IRIS has a multitude of users.	
4	2, Preamble	xvii	The text on Systematic Review Protocols states that they may change during the course of the assessment. We can understand why additional search strategies might be added for example, but are having difficulty imagining situations where other existing protocols would warrant a change.	Please reconsider this statement and provide examples of changes to protocols that might be made during a course of an assessment or perhaps provide examples of changes in science questions that may require a change to protocols.	S
5	4, Preamble	xvii - xviii	Much detail regarding evaluation of study quality was removed from the Preamble in favor of noting EPA guidance, although without citations provided for them, and also by stating that study evaluation criteria will be posted on the IRIS website. We presume the latter statement is referring to the Preliminary Materials that are developed for each chemical. However, when we looked at the most recent set of Preliminary Materials, those for Dibutyl	Suggest reconsidering the current text regarding study quality and add back in the details that were deleted. We saw the previous text to be more transparent.	S/M

			Phthalate dated January 2015 we did see evaluation criteria described but no citations to EPA Guideline documents so it is confusing how the factors that the Preamble states are used to judge study quality, are actually used together.		
6	4, Preamble	xviii	The meaning of "..effects that are more important or studies that are more informative.." is not clear.	Consider more precise terms, perhaps an example substitute for “important” is biologically significant, we are not sure what is meant by “informative”.	S
7	5, Preamble	xix, line 19	"If there is credible evidence of carcinogenicity, an assessment determines whether the mode-of-action involves mutagenicity, because this influences the approach to dose-response assessment and subsequent application of adjustment factors for exposures early in life." This statement isn't precise. All cancers have mutations, so that if the MOA only has to "involve" mutagenicity, all cancers would have a mutagenic MOA, and this classification for distinguishing carcinogens in EPA's 2005 supplementary guidance would have no utility. As the Risk Assessment Forum draft document on mutagenic MOA, and several subsequent publications support, the mutagenicity must be caused by the chemical or an immediate metabolite and must be one of the first key events in the MOA.	Please correct.	S

8	5, Preamble	xviii, line 39	"Each synthesis considers aspects of an association that may suggest causation: consistency, exposure-response relationship, strength of association, temporal relationship, biological plausibility, coherence, and “natural experiments” in humans."	Suggest beginning this sentence with "As discussed more completely in the 2005 Cancer Guidelines..."	S
9	7, Preamble	xix, line 77	Reference values for other than chronic exposures are not mentioned.	Suggest including acute and subchronic here.	S
10	7, Preamble	xx, line 12	"With complex data, an assessment may develop specialized exposure-response models if compatible with the scope of the assessment." It would be useful and save comments and time later, if EPA committed to an external review of any novel exposure-response models before and independently of the external review of the draft IRIS document. We believe this would also be consistent with the SAB recommendations on review of models.	Please indicate that there will be an external review of any novel exposure-response models before and independently of the external review of the draft IRIS document.	S
11	7, Preamble and General Preamble	xx, Line 58	It is not evident why the phrase "Calculation of reference values starts with a point of departure, generally for an early effect that precedes overt toxicity." is qualified by early effects that precede over toxicity. This is not described in the EPA RfD/RfC guidance and seems to run counter to the recommendations by the SAB in their review of the Preamble.	Recommend distinguishing additional requirements or procedures that are under discussion to include in future guidance as recommended by the SAB.	S/M
12	9, Preamble	xxi, line 94	"The Preface specifies the scope of an assessment and its relation to prior assessments." This statement implies that the	For clarity and transparency, please add a sentence that states that the Preface describes the process that will be followed for chemicals	S

			process described in the Preface to the document to which it is attached was followed for that chemical. However, we have been told that the legacy chemicals did not necessarily follow the process as stated in the Preface.	that begin the IRIS evaluation contemporaneous with that version of the Preface.	
13	3, Preamble	xvii, line 59	"IRIS assessments go beyond standard practices of systematic review in including pertinent studies." Such an assertion suggest that either a reference or examples should be included.	Suggest deleting this sentence.	S
14	Preamble	General	The Preamble has been significantly revised. While the SAB CAAC made many suggestions for change in this section, some of which were incorporated and some that have not, we don't believe they have been reviewed to determine 1) whether they have been reviewed for consistency with EPA guidelines and guidance, 2) to determine whether procedures that are currently not in guidance or policy are designated as "under discussion" as such 3) to determine whether the Preamble represents what was done for the TMB analysis and 4) to determine whether the SAB agrees with removal of references from the Preamble though they clearly suggested they should be included.	We believe the Preamble should be a separate document that is revised and reviewed independently of any specific chemical's review.	S/M
15	Executive Summary	xxviii, line 18	"Dividing the HED [of 3.01] by this composite UF of 300 yielded an RfD of 1 x 10-1 mg/kg-	Please correct.	S

			day" We believe the value should be 1 x 10-2 mg/kg-day.		
16	Executive Summary	xxix, line 12	"Dividing the POD for hematological effects (3.01 mg/kg-day) and neurotoxicity effects (3.5 mg/kg-day) by the composite UF of 100 results in an RfD of 3 x 10-2 and 4 x 10-2 mg/kg-day for decreased monocytes and decreased pain sensitivity, respectively." While we understand the rules of rounding up or rounding down numbers, we find it difficult to explain scientifically why the same PODs divided by 300 result in identical chronic RfDs but divided by 100 result in subchronic RfDs that differ by (1/4 =) 25%.	Suggest an explanation be added for this logical inconsistency.	S
17	Appendix A	A-3	The response the SAB comment states that "text was also added to the Preface to describe where approaches in the TMB assessment differ from those outline in the Preamble." However this was not clearly stated in the Preface, it states that approaches were used which were available at the time (2012) and a problem formulation and protocol development began in 2015 with other assessments. It seems that the reader is to believe that all other aspects of the TMB assessment are consistent with procedures described in the Preamble as it is not stated. There is not mention at all of the Preamble in the Preface let alone procedures described therein.	If there are any other approaches that differ for TMBs they should be mentioned in the Preface, or if not it should be so stated in the Preface.	S

18	Appendix A	A-11	The public comments are not fully addressed here.	In the response to GC.4-1 regarding public comments it seems relevant to note the Appendix F is not in the final version of the assessment and possibly note the rationale. We believe that it would be most transparent and consistent with the IRIS Process to bring the public comments and responses into the final version of the TMB assessment as an Appendix and recommend that EPA do so.	S
20	2.1.2.	2-8, line 15	Of the study selected, EPA states "no information is available regarding the change in these responses that would be considered biologically significant." Yet in the supplemental information for this document (page A-14), it is stated: "It is EPA's practice that evaluation of evidence should first consider biological significance to the extent possible". It appears, therefore, that EPA may not be following its own "practice". Since the reference for the practice is not provided, we can't verify how EPA considers the relative importance of statistical significance and biological significance.	Please reconcile these statements. In addition, since the assessment states that EPA has a "practice" with regard to biological significance, we would appreciate a copy or citation of that practice.	S
21	Executive Summary and Section 2.2	xxvi - xxix	The subchronic reference values are not as easy to quickly find as the chronic values in the Executive Summary. This also applies to the subsections of Section 2.1, but is especially important for the IRIS Summary which we understand will be identical to this Executive Summary.	The subchronic RfC should be clearly stated and bolded similar to the chronic RfC.	E

22	Section 2.2 and Executive Summary	General	It is not clear why developmental and maternal endpoints are discussed and presented in the development of both chronic and subchronic reference values. It seems that in comparison they would be more relevant for the shorter timeframe and less relevant for the chronic timeframe.	Suggest explaining the utility of the chronic developmental reference values versus the subchronic values.	S/M
23	Section 2.2 and Executive Summary	General	The intended use of the developmental and maternal organ specific reference values are not clear. Averaging time is an important consideration for using RfCs and EPA's guidance for inhalation risk assessment (RAGS part F) states that "to the extent possible exposure durations (EDs) evaluated in a site-specific risk assessment should be consistent with the ED represented by the toxicity value." If one had women of child bearing age in a population it is not clear how the values would be applied, and though the number is the same whether one should say they are applying the chronic or subchronic value.	Suggest providing a citation or some guidance on the use of the maternal and developmental organ specific reference values, especially the reference concentration. It is not clear whether they would apply throughout gestation, possibly longer, or whether there is another critical timeframe that should be considered.	S/M